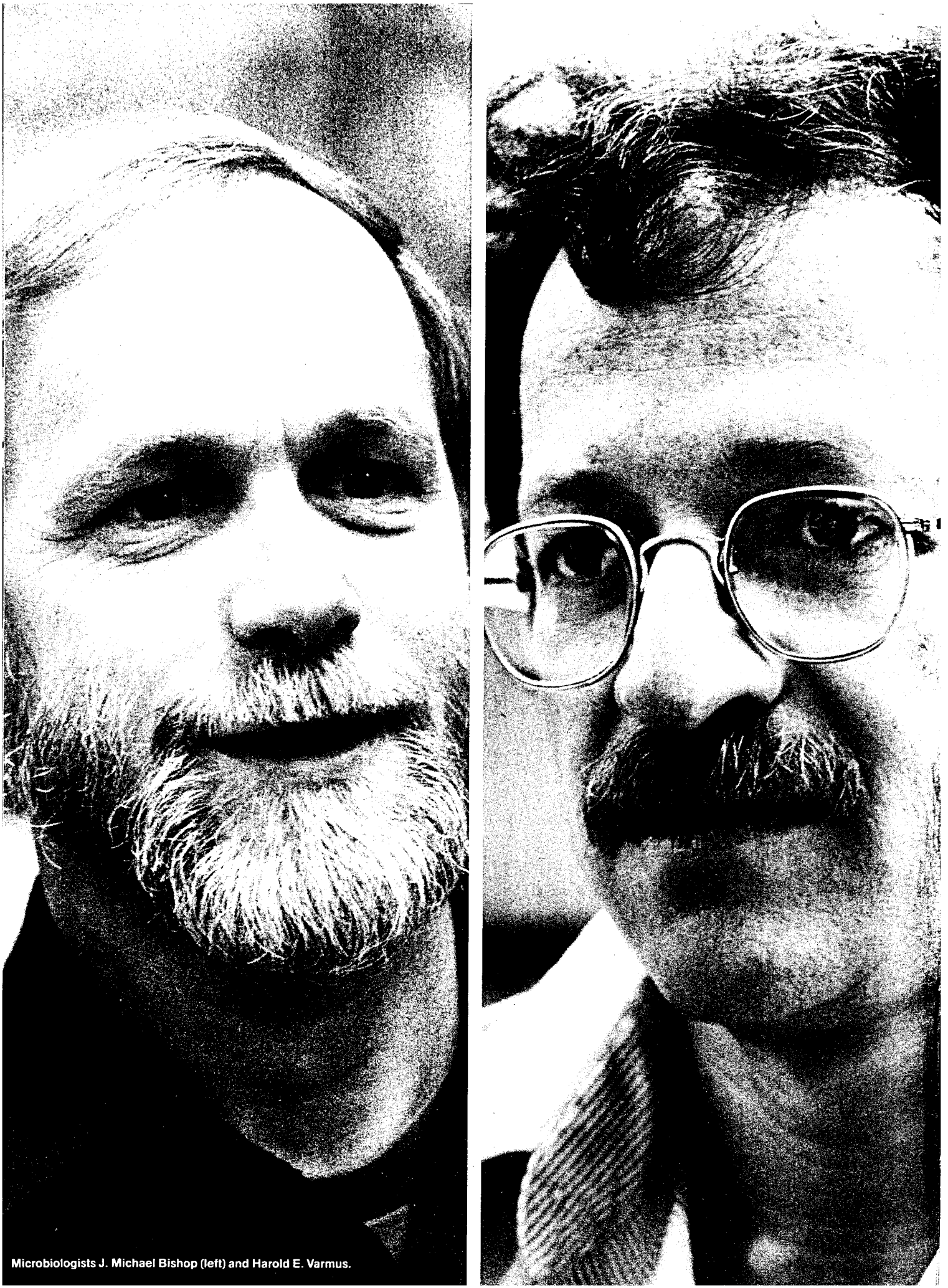


Microbiologists J. Michael Bishop (left) and Harold E. Varmus.

The Hunting of the src

Microbiologists Varmus and Bishop also work with retroviruses, and the two together have played a large part in making these viruses one of the most fruitful tools yet in cancer research. Not long after his arrival at UCSF in 1968, J. Michael Bishop switched from study of the polio virus to study of the large family of RNA tumor viruses called retroviruses, then largely an enigma.

"We knew nothing at the time about retroviruses," Bishop says, "and they seemed to be a large challenge. I began my research simply out of a fundamental interest in how the viruses worked, and it was only after a few years that it became obvious that they would be a useful tool in the study of cancer.

"One important lesson we've learned is that you *do* learn useful things from basic research."

In 1970 Harold Varmus joined Bishop in his investigation of these viruses, and since then much of their work has been published in collaboration. This work won for the two researchers the California "Scientists of the Year" award.

The retrovirus with which they first worked is called Rous sarcoma virus. Other researchers had isolated it from a chicken tumor, and a specific gene—named *src,* after sarcoma—was identified as being responsible for causing the tumor. The entire viral DNA becomes part of the host DNA, and the *src* gene takes advantage of the production machinery in the cell to make many copies of a particular protein, at the same time turning the cell into a cancer cell.

Work carried out at UCSF and elsewhere led to the identification of the protein specified by the *src* gene as a "kinase"—an enzyme that chemically alters certain of the amino acids in proteins. This was the essential first step in determining the specific proteins this enzyme affects, and ultimately the function of these proteins.

The latter information could well reveal how the *src* gene turns normal cells into cancer cells, and Bishop is currently hard at work on this problem.

One of the major contributions of Varmus and Bishop was their discovery that these retrovirus "oncogenes," or cancer-causing genes, have nearly identical counterparts in the DNA of normal animal cells, from human beings to fish. The hypothesis of Bishop and Varmus is that these retroviruses picked up normal genes from animal cells during the course of their evolution, and somehow altered them so that, when they are reinserted into animal cells, they induce cancer.

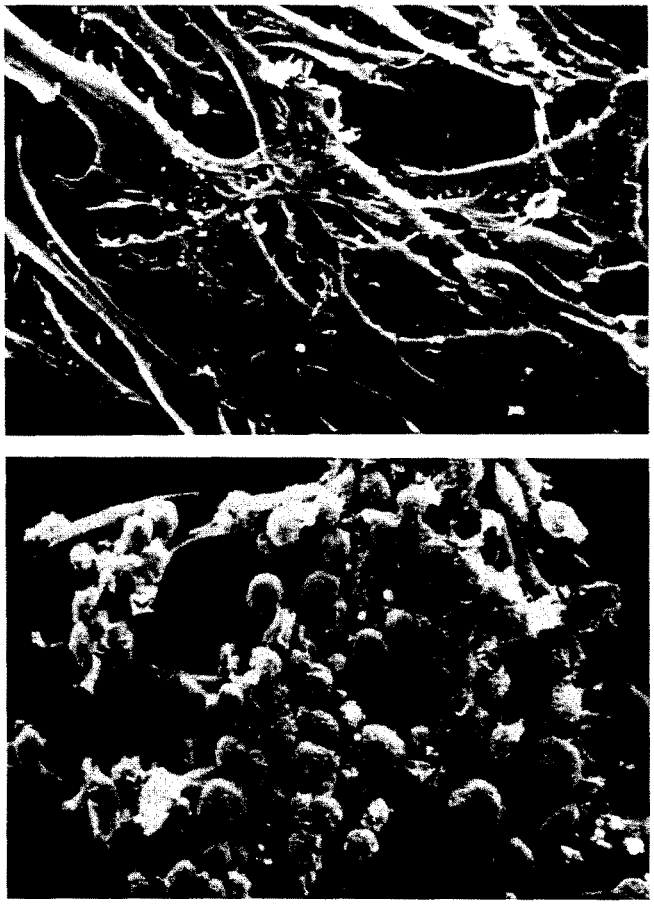
So far, seventeen distinct viral cancer genes have been identified that are closely related to, and presumably derived from, a cellular gene.

These findings suggest that perhaps the oncogenes found in normal cells have a necessary function in the cell, but that some agent—a carcinogen or a viral gene stuck next door to the oncogene—disrupts this function to induce a tumor. Researchers have in fact shown that three oncogenes isolated from normal mice and rat cells can cause cancerous growth in cell cultures.

"We believe that cellular oncogenes do the same thing as viral oncogenes, and that here we have a fundamental mechanism by which cancer arises," Bishop says. "There may be lots of triggers, but I think there are only a limited number of ways by which a tumor arises—that's *the* great puzzle."

Varmus and Bishop are working to demonstrate that cellular oncogenes are at the heart of carcinogenesis.

Certainly the existence of cancer genes that are normal genes, but somehow subverted, could go a long way toward explaining how so many agents lead to cancer.



Transformation of cultured cells by the Rous sarcoma virus is apparent in scanning electron micrographs made by G. Steven Martin of the University of California, Berkeley. Normal fibroblasts, or connective-tissue cells, adhere to the surface of a laboratory dish in which they are cultured and have a flat, extended configuration (above). On infection by the Rous sarcoma virus, the cells become round instead of flat and cluster together in piles (below), presumably because cell proteins are altered by the enzyme encoded by src.

Jumping Genes

The ability of retroviruses to move from one cell to another makes them look suspiciously like a number of "jumping genes" that researchers have started turning up in the genetic material of animals and plants. The old notion that chromosomes are essentially stable creatures has been evaporating. Genes can move around, and apparently viruses have learned to take advantage of this.

"Jumping genes" are mobile genetic elements that were first detected in corn more than 30 years ago, but were mentally shelved as genetic oddities. In the late 1960s it started to become apparent that they were not.

Geneticist Ira Herskowitz has done pioneering work, first at the University of Oregon and since last year at UCSF, in elucidating just how genes can jump around.

Herskowitz and his colleagues are investigating the mechanisms by which cells of baker's yeast give rise to descendants of the opposite sex. Yeast are single-celled organisms whose cells come in three types: two of which, called mating types, are equivalent to the two sexes; while the third type, which results from mating of the other two, does not itself mate.

The three cell types are a kind of specialization, analogous to the specialization of cells in higher organisms, and they provide a simple, easy-to-handle model for the study of cell differentiation. The sex of a particular cell is determined by a single gene, with two alternatives for the gene determining the two sexes (the third type, which doesn't mate, has both genes).

Normally, one would expect each type of cell to produce only "daughters" of its own type, or sex, when it reproduces vegetatively—i.e., by dividing into two cells. And in fact, normal yeast cells produce progeny of the opposite sex very rarely, only about one time in a million. But in other strains of yeast, the story is very different. In one such strain, cells switch their sex nearly every generation—cells of one sex will produce offspring of the opposite sex, which in turn will produce offspring of the original sex, and so on.

What could account for this rapid switching of genes?

Detective work by Herskowitz and his co-workers unraveled the mystery. Because all yeast cells evidently have the potential to be of either sex, Herskowitz suggested that all yeast must have copies of both sex genes, but that these genes are silent. They are stored in separate places on the chromosome in an inactive state, and only when they are shifted to a third site on the chromosome—called the mating-type locus—are they activated to determine the sex of the yeast cell.

A copy of one or the other silent, stored mating genes is made, and this copy "jumps" to the mating locus and is turned on. Herskowitz calls this model the "cassette model," the jumping genes "cassettes," and the mating-type locus to which the genes must "jump" to be activated the "playback" locus—likening them all to a tape recorder with interchangeable cassettes.

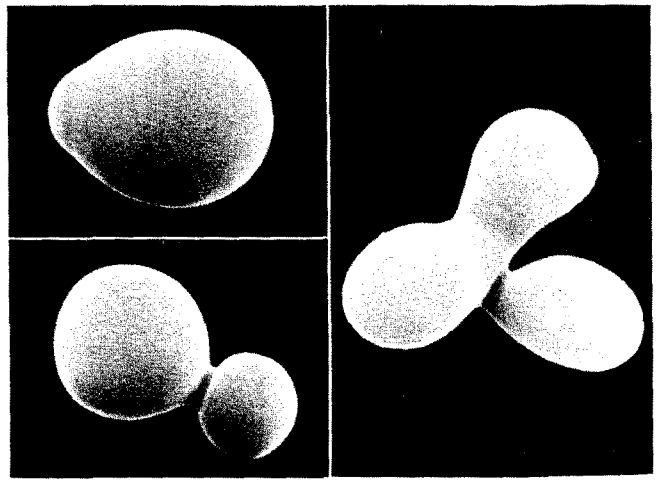
This legerdemain is not restricted to yeast. Researchers have found that the microorganism that causes sleeping sickness can also juggle the genes for its protein coat, allowing it to make more than 100 different coats to outmaneuver the body's immune system defenses against it.

"All this is part of the overall revolution in thinking about genetics," says Herskowitz, whose research centers around how these mating genes determine the sex of the cell and how the mating genes are juggled.

"The thinking in the field has been dominated by the idea, originated in the early '60s, that regulatory proteins turn genes on and off, and the even earlier dogma that genetic information is absolutely fixed. We have shown that you can activate genes by moving them around.

"Varmus, for example," Herskowitz says, "has shown that, if you insert viral DNA next to a gene, you can turn up the expression of that gene. Likewise, Varmus and Bishop's *src* gene becomes overactivated, and thus an active oncogene, when it gets picked up by a virus and reinserted into a chromosome. And now there may be switchable cassettes—movable blocks of coding information.

"Keith's [Yamamoto] work with steroid hormones shows that the earlier view of how genes are turned on and off is still correct, and the cassette model may turn out not to deserve equal billing with it, but you have to consider it as a possible genetic mechanism," Herskowitz says. "It hasn't been part of our thinking in the past—but now it is."



A typical cell of baker's yeast (left) and another yeast cell giving rise to a daughter by budding (bottom). When two cells of opposite sex mate, they form a zygote. The zygote is a third type of yeast cell that does not mate, but can give rise to a daughter yeast cell by budding (right).